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ROTHWELL, FIGG, ERNST & MANBECK, P.C.
1425 K STREET, N.W.
SUITE 800
WASHINGTON, DC 20005

EXAMINER	
KAPUSHOC, STEPHEN THOMAS	
ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/628,554	COMINGS ET AL.	
	Examiner	Art Unit	
	Stephen Kapushoc	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1-6-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase 'survival time' (preamble of claim 1) renders the claims unclear because the claimed method does not in fact predict an absolute survival time. The method predicts a relative time of survival for a subject possessing a mutation versus a subject not possessing a mutation. The claim may be more clear if edited to read 'relative time of survival' instead of 'survival time'. See MPEP § 2173.05(b).

3. Claims 1-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase 'reduced survival' (part (b) of claim 1) renders the claims unclear because while the phrase contains a term of degree (reduced meaning less than), the claim does not provide a basis for measure to determine whether or not survival is in fact reduced. Because the measure is relative, the claim should provide a standard for comparison. The claim may be more clear if edited to include 'as compared to the time of survival of a subject having multiple sclerosis but not having the mutation' at the end of the claim. See MPEP § 2173.05(b).

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for predicting time of survival in human subjects having multiple sclerosis (MS) wherein the presence of the CCR5 delta 32 mutation in a subject with MS is predictive of a reduced time of survival as compared to a subject having MS but not possessing the CCR5 delta 32 mutation, does not reasonably provide enablement for the analysis of any non-human subjects or the use of any CCR5 mutation other than the delta 32 deletionmutation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Nature of the invention and breadth of the claims

The claims are drawn to a method for determining the survival time of a subject with MS. The method comprises detecting the presence of a mutation in the CCR5 gene, wherein the mutation correlates to reduced time of survival in subjects having MS.

The claims encompass determining the survival time of any subject organism having MS that possesses a CCR5 gene. Claims 1 and 4 encompass the detection of any type of mutation in the CCR5 gene. Such mutations include but are not limited to any type of single base or multi-nucleotide transitions and

transversions (including silent mutations), any single base or multi-nucleotide insertions or deletions, and any type of gene rearrangement anywhere within the coding, non-coding, or regulatory region of the gene. Claims 2 and 4 create the limitation that the detected mutation is a deletion, and encompass any deletion of any number of nucleotides from anywhere in the CCR5 gene. Claims 3 and 6 create the limitation that detected mutation in the CCR5 gene is the delta 32 deletion mutation.

The nature of the invention requires knowledge of a correlation between CCR5 gene mutations and the relative survival time of a subject having MS.

Direction provided by the specification and working examples

The specification teaches an example of the analysis of the CCR5 delta 32 mutation in DNA isolated from post-mortem human brain tissue from 132 MS cases (p.6). The specification teaches that survival analyses were used to test the effect of the CCR5 delta 32 deletion survival (p.7). The specification teaches that there is a significant association between the CCR5 delta 32 deletion allele (allele 2) with early death. When the subject genotypes were analyzed according to placement into one of five groups based on years of survival after disease onset (≤5 yrs, 6-10 yrs, 11-15 yrs, 15-20 yrs, and ≥21 yrs), subjects lacking a copy of the CCR5 delta 32 deletion allele survived progressively more years as compared to subjects possessing at least one copy of the delta 32 deletion mutation allele of the CCR5 gene (p.7; p.10 Table 1). The specification teaches that the analysis reveals that MS patients with at least one copy of the delta 32 CCR5 allele (the 12 and 22 genotypes) have over twice the mortality as

compared to the 11 genotype (subjects not having a copy of the delta 32 CCR5 deletion mutation).

The specification does not provide any teachings or examples directed toward non-human subjects.

The specification does not provide any analysis of any mutations other than the delta 32 deletion mutation of the CCR5 gene.

The specification does not offer any external validation of the alleged correlation between the CCR5 delta 32 mutation and survival time. The specification does not teach the successful application of the methods to any population other than those in which the asserted correlation was established. It is therefore unknown if the CCR5 delta 32 deletion mutation would be predictive of relative survival time in MS patients in any other population.

State of the art, level of skill in the art, and level of unpredictability

While the level of skill in the art of identifying genetic mutations is quite high, there is a high level of unpredictability with regard to any given mutation being associated with a particular phenotype or disease course. There is also a high degree of unpredictability with regard to the use of any specific mutation in one organism as a prognostic indicator of a phenotype in any other different organism. Additionally, the prior art indicates the unpredictability in using the CCR5 delta 32 deletion mutation as an indicator of relative survival time in subjects with MS.

There is a large body of knowledge in the prior art related to mutations and polymorphisms in general, and their association with specific phenotypes

including disease states. However, the art is highly unpredictable with regard to the functionality of a given genomic mutation. After a mutation is identified, it is unpredictable whether any such mutation would be associated with any phenotypic trait such as a disease state in every population. For example, Hacker et al teaches that they were unable to confirm an association between a gene mutation and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (Gut, 1997, Vol. 40, pages 623-627).

Additionally, it is entirely unpredictable whether or not the CCR5 gene of any other organism would contain mutations homologous to the delta 32 deletion mutation described in the instant specification for the human CCR5 gene (p.4), and whether or not such mutations would be indicative of any particular disease course. The unpredictability of the interspecies conservation of mutation sites is demonstrated in the prior art of Mummidi et al (2000). Mummidi et al teaches the sequence analysis of the CC chemokine receptor 5 (CCR5) gene in humans and non-primates. Notably, the reference teaches that some positions that contain mutations in the human gene do not have mutations in other non-primate animals, and vice versa (p.18950, Fig 1).

The specification provides no guidance or examples of CCR5 mutations in any organisms other than humans. While it is generally held true that structure correlates with function, Bork et al (1993) teaches an analysis of sugar kinases, and indicates that very distinct proteins (with different three-dimensional structures and strikingly different sequence patterns) can catalyze chemically

equivalent reactions of similar or identical substrates (P.31 - Abstract). Thus a CCR5 gene in one organism may be quite dissimilar to the human CCR5 gene described in the instant specification.

Similarly, the converse line of reasoning demonstrates that just finding a gene similar to the human CCR5 gene in an animal other than a human does not necessarily mean that a mutation in the gene will be predictive of disease course. It is possible that an apparent CCR5 homolog in a non-human animal might not be functionally equivalent to the CCR5 gene in humans. Such a possibility is exemplified by Jüppner (1995), which teaches that despite significant structural conservation, rat, opossum, and human PTH/PTHrP receptor homologs display distinct functional characteristics (Abstract; pp.39S-40S). Thus, even if putative homologs of the CCR5 gene are identified and sequenced in other animals, and even if these new CCR5 genes display mutations, one would have to perform a large amount of experimentation to determine whether or not these putative mutations would be indicative of any particular disease course the animals.

The prior art specific to the CCR5 delta 32 deletion mutation and relative time of survival also indicates the unpredictability of using the presence of the CCR5 delta 32 deletion as an indicator of a shorter relative time of survival. Sellebjerg et al (2000) (as cited in the IDS) teaches an analysis of the CCR5 delta 32 mutation as it correlates to several parameters of disease course in subjects with MS. Sellebjerg et al teaches that the age of onset of disease is lower in patients carrying the delta 32 deletion mutation of the CCR5 gene than in the remaining patients (p.100 – Results *3.1 CCR5 Δ32 in patients and control*

subjects). Midgard et al (1995) (as cited in the IDS) teaches an analysis of several prognostic factors for survival time in MS. Midgard et al teaches that the shortest survival is in patients with a high age at onset (p.418 – Results; Table 1). Taken together, these references would indicate that the delta 32 deletion mutation of the CCR5 gene is indicative of a longer relative survival time.

Quantity of experimentation required

A large and prohibitive amount of experimentation would have to be performed in order to make and use the invention in the full scope of the claims. Such experimentation would include the identification of the CCR5 gene in any organism of interest, as well as identification of any possible mutations within the newly identified gene. Use of the invention in any organism other than humans would also require validation of any identified mutations to prove that they are in fact predictive a shorter relative time of survival. Because several of the claims encompass the analysis of any mutation of the CCR5 gene, use of the invention would require a complete sequence analysis of the entire subject gene.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and the breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the amount of guidance by the applicant and the paucity of working examples, it is the conclusion the an undue amount of experimentation would be required to make and use the invention claimed invention.

6. Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to the presence of any mutation in a CCR5 gene (claims 1 and 4), any deletion mutation in the CCR5 gene (claims 2 and 5), and a delta 32 deletion mutation in the CCR5 gene of any organism (claims 3 and 6), 'wherein the mutation correlates to reduced survival of subjects having multiple sclerosis'. The claims encompass the analysis of a very wide variety of mutations from any portion of the CCR5 gene from any organism, including but not limited to single base or multi-nucleotide transitions and transversions, insertions and deletions, and chromosomal rearrangements.

The application provides an example only of the analysis of the CCR 5 delta 32 mutation in human subjects as detected by PCR (paragraph [0026]). The application does not demonstrate the nature of any other CCR5 mutations from human subjects, nor any CCR5 mutations from any non-human organism. The specification does not provide an explanation of how any CCR5 mutation is functional with regard to the prediction of survival time of a subject having MS.

Given the broad range of possible mutations and their unique structural nature, the specification provides no relevant identifying characteristics of any particular mutation that would suggest a particular mutation would be useful to indicate that a subject with MS will have a shorter relative survival time. The

CCR5 delta 32 mutation taught in the specification is not representative of the broad range of potential mutations encompassed by the claims; nor is the mutation predictive of the other mutations that would be included in the claimed invention. The claims are inclusive of an unlimited number of additional mutations in human as well from non-human organisms, however the specification does not disclose a sufficient description of characteristics that would permit the identification of a mutation that indicates that a subject with MS will have a shorter relative survival time. Furthermore the specification does not provide any correlation between the structure (e.g. nucleotide sequence or position within the gene) and function (i.e. indicative of a shorter relative survival time) for any additional mutations, the detection of which are encompassed by the claims, because the structure of such mutations is entirely unknown.

Additionally, the claims are drawn to the analysis of any subject organism possessing a CCR5 gene. However, a homologous or functionally equivalent mutation in the CCR5 gene of a non-human organism may not be readily identifiable as a 'CCR5 delta 32' mutation. Even if the observed mutation is a deletion of 32 nucleotides, the mutation may not be homologous or functionally equivalent to the 'CCR5 delta 32' mutation of the human gene described in the specification and the prior art.

Thus, having considered the breadth of the claims and the provisions of the specification, it is concluded that the specification does not provide adequate written description for the claims.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

9. Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barcellos et al (2000) (as cited in the IDS) in view of Midgard et al (1995) (as cited in the IDS).

Barcellos et al teaches the analysis of the CCR5 gene in a population of 125 families with multiple case of MS including 322 affected individuals (p. 283 - Results). The reference teaches obtaining samples from the individuals (white blood cells transformed into lymphoblastoid cell lines) (p.282 – *Genotyping*). Barcellos et al teaches that age of onset was approximately 3 years later in patients carrying the CCR5 delta 32 deletion (p.281 – Abstract; p.284 – Table 3).

Barcellos et al does not specifically teach that the CCR5 delta 32 deletion correlates to a reduced survival time in subjects having MS versus subjects having MS who do not posses the CCR5 delta 32 deletion.

Midgard et al teaches an analysis of several prognostic factors for survival time in MS. Midgard et al teaches that the shortest survival is in patients with a high age at onset (p.418 – Results; Table 1).

It would have been prima facie obvious to one of skill in the art at the time the invention was made to have combined the method and results of Barcellos et al with the teachings of Midgard et al to reach the conclusion that the presence of the CCR5 delta 32 deletion mutation in a subject with MS is predictive of a shorter survival time versus a subject that does not possess the CCR5 delta 32 deletion mutation. One would have been motivated to combine these methods and results in order to expand the amount of information provided by analysis of the CCR5 gene in subjects with MS. One would have had a reasonable expectation of success because both Barcellos et al and Midgard et al utilized populations of subjects with MS.

10. Claims 4-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barcellos et al (2000) in view of Midgard et al (1995) as applied to claims 1-3 above, and further in view of Cohen et al (2001) US Patent 6,265,546.

The teachings of Barcellos et al in view of Midgard et al are applied to claims 4-6 as they were previously applied to claims 1-3.

Barcellos in view of Midgard does not teach the use of whole blood to obtain a sample for genetic analysis.

Cohen et al teaches methods for the genetic analysis of disease related genes. Cohen teaches sources for obtaining DNA for genotyping analysis. Specifically, Cohen teaches that whole blood is a useful source of DNA for genotyping analysis, and recommends peripheral venous blood as a preferred source of genomic DNA for genotyping (col. 96 lns.10-33).

It would have been prima facie obvious to one of skill in the art at the time the invention was made to have modified the methods of Barcellos et al in view of Midgard et al to have used DNA from whole blood as taught by Cohen et al. One would have been motivated to do so in order have an additional source of genetic material for the analysis of the CCR5 gene in subjects with MS. One would have had a reasonable expectation of success because Cohen et al teaches that the DNA from whole blood is suitable for genotyping analysis.

Conclusion

No claim is allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached at 571-272-0745. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen Kapushoc
Art Unit 1634

JULIET C. SWITZER
PRIMARY EXAMINER